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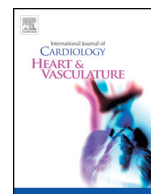
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Association of carotid intima-media thickness with exercise tolerance test in type 2 diabetic patients

Ali Momeni^{a,*}, Abdolmajid Taheri^b, Maryam Mansuri^c, Ali Bazdar^a, Morteza Sedehi^d, Masoud Amiri^e

^a Internal Medicine Department, Shahrekord University of Medical Sciences, Shahrekord, Iran

^b Radiology Department, Shahrekord University of Medical Sciences, Shahrekord, Iran

^c Shahrekord University of Medical Sciences, Shahrekord, Iran

^d Health school, Shahrekord University of Medical Sciences, Shahrekord, Iran

^e Department of Epidemiology and Biostatistics, Shahrekord University of Medical Sciences, Shahrekord, Iran

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ABSTRACT

Aims: Atherosclerosis and ischemic heart disease are more common in diabetic patients. Atherosclerosis process can disturb the normal functioning of the vascular endothelium and increase vessel wall thickness. The aim of this study was the comparison of Carotid intima-media thickness (CIMT) with Exercise tolerance test as an alternative way to evaluate cardiac ischemia in diabetic patients.

Methods: In a cross-sectional study, 30 diabetic patients with positive exercise test and 30 diabetic patients with negative exercise test were enrolled. CIMT of the carotid artery in both groups of patients was measured.

Result: CIMT in the patients with positive and negative exercise test were 1.04 ± 0.21 mm and 0.61 ± 0.11 mm, respectively ($P < 0.001$). CIMT in positive exercise test group was positively associated with age and negatively associated with gender, FBS, HDL and LDL cholesterol and in negative exercise group was negatively associated with gender, age, FBS, HDL and LDL cholesterol.

Conclusion: Considering observed significant positive association between CIMT with result of exercise tolerance test (ETT) in type 2 diabetic patients, it may possible to use CIMT as an inexpensive and non-invasive method for evaluation of ischemic heart disease in diabetic patients.

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1. Introduction

Diabetes mellitus is one of the most important and common causes of chronic kidney disease (CKD), atherosclerosis and coronary artery disease (CAD) [1]. Two major diabetic complications are micro-vascular and macro-vascular diseases. Micro-vascular complications of diabetes are neuropathy, nephropathy and retinopathy [2]; however, macro-vascular complications of diabetes such as ischemic heart disease (IHD) and myocardial infarction (MI), diastolic cardiac dysfunction, sudden cardiac death, peripheral artery disease and cerebrovascular disease are common in diabetic patients and could be responsible for increasing rates of morbidity and mortality in these patients [3–7].

Some factors have been mentioned as risk factors of generalized endothelial dysfunction and vasculopathy in diabetic patients. Hypertension is a common comorbidity in diabetes, so about 70% of type 2 diabetic patients have hypertension, which may result in endothelial dysfunction, vascular layer remodeling and increasing of arterial wall thickness [8]. Renin-angiotensin aldosterone system has also a major role in the progression of vascular remodeling and diabetic

vasculopathy; in fact, angiotensin II could increase the production of growth factors and reactive oxygen species leading to endothelial dysfunction and progression of atherosclerosis [9]. Hyperglycemia could also damage the vascular wall via production of advanced glycation end products (AGEs) and oxidative stress [10]. In addition, cytokines may also play an important role in producing of endothelial dysfunction and vascular damage in diabetes [11].

Moreover, one of the most important types of diabetic vasculopathy is cardiovascular disease (CVD), that some predisposing factors for development of CVD could be chronic hyperglycemia and AGEs, insulin resistance, oxidative stress and chronic low grade inflammation [2,12]. Hyperlipidemia is also prevalent among diabetic patients which may increase the risk of cardiovascular complications [13].

Electrocardiography, Echocardiography, exercise test, cardiac nuclear scan and angiography are used for evaluation of ischemic heart disease (IHD) in diabetic patients [14–16]. Furthermore, coronary angiography is the most accurate method for assessment of IHD, but it is invasive and has some complications [17]. Exercise tolerance test (ETT), however, is a noninvasive, practical and inexpensive and relatively accurate test for evaluation of IHD [18]. Some indications of ETT are indeed the assessment of chest pain in the patients with moderate risk of IHD, risk assessment after MI, evaluation of therapeutic response after

* Corresponding author at: Hajar Hospital, Shahrekord, Iran.
E-mail address: ali.momenydr@gmail.com (A. Momeni).

revascularization or medical treatment and preoperative cardiac risk assessment. However, ETT has also some limitations; for example, it is contraindicated in the patients with acute myocardial infarction (AMI), aortic dissection, severe aortic stenosis, acute pulmonary embolism or infarction and severe heart failure [19]. ETT may also lead to MI or death in about 0.04% of cases [20].

Carotid artery intima media thickness (CIMT) is the distance between intima layer and adventitial layer of carotid artery and measures by M-mode ultrasonography which has been used for evaluation of presence and severity of atherosclerosis [21]. Increasing CIMT could be due to hypertrophy of intima, media or two layers. CIMT can also be measured at the site of common carotid artery, bifurcation of carotid artery or proximal site of internal carotid artery, in the right side or mean value of bilateral right and left side [22]. Moreover, in middle age patients, mean CIMT of 0.6–0.7 mm are usually considered as normal and CIMT value >1 mm is a marker of atherosclerosis and probably IHD [23].

Measurement of CIMT is a sensitive and probably specific method for evaluation of atherosclerosis and further cardiovascular and cerebrovascular diseases [24]. CIMT may be also associated with microvascular complications of diabetes such as retinopathy [25]. However, there are some studies about association of CIMT with occurrence of coronary artery event; for example, Salonen and colleagues, in the study on 1288 patients reported two fold rising of acute coronary events in patients with higher CIMT [26].

The aim of the study was the evaluation of the results of ETT as an index of IHD and CIMT as an indicator of generalized atherosclerosis in the type 2 diabetic patients.

2. Methods and materials

In a cross-sectional study, 60 type 2 diabetic (T2DM) patients in two equal groups of 30 patients with positive ET and 30 patients with negative ET were enrolled. At first, the records of the patients who recently had angiography were evaluated, and 30 diabetic patients with positive and 30 diabetic patients with negative ETT who fulfil inclusion and exclusion criteria were selected and enrolled in the study. Inclusion criteria were T2DM patients, ability to do the ETT completely, and exclusion criteria were: history of IHD such as MI, cardiac angina, ST-T change, left bundle branch or atrial fibrillation in the ECG, severe valvular heart disease before ETT, and lack of cooperation during the study.

During ETT, heart rate, ST-T change and metabolic equivalent (METs) were evaluated and ST suppression >1 mm was considered as positive result. Some criteria for discontinuation of ETT were ST elevation, reduction of systolic blood pressure >10 mm/Hg, ventricular tachycardia or other life threatening ventricular arrhythmia, chest pain, vertigo and severe fatigue or inability for continuation of procedure.

In addition, ETT was considered as incomplete and patients excluded from study if 85% of maximal heart rate (220 minus age) not achieved.

Demographic characteristics of patients such as age, body mass index (BMI), duration of diabetes and laboratory data like fasting blood sugar (FBS) and LDL cholesterol were measured. In all patients, CIMT was measured at the 2-cm distance of the right common carotid bifurcation, in the supine position, using a Doppler ultrasonography device (Siemens G50, Germany) with linear multi-frequencies of 7.5- to 10-MHz probe by the same sonographer, so he did not know the results of ETT of the patients. All data were collected and were entered to SPSS (version 20.0, SPSS Inc., Chicago, IL, USA) and evaluated by using *t*-test and Pearson test. All continuous variables were mentioned as mean \pm standard deviation and $P < 0.05$ was considered as statistically significant. All information was kept confidential, and informed consent letter was taken from all patients, at the beginning of the study. The study was funded by the Research and Technology Deputy of the Shahrekord University of Medical Sciences, Shahrekord, Iran. The study protocol was approved by the Ethics Committee of the Shahrekord University of Medical Sciences with No 172.

Table 1

Mean \pm standard deviation of CIMT in the positive and negative patients.

Group		Positive ET		Negative ET
CIMT (mm)		1.04 ± 0.21		0.61 ± 0.21
P	<0.001			
Sex	Male	Female	Male	Female
CIMT (mm)	98 ± 22	1.08 ± 0.20	0.63 ± 0.14	0.60 ± 0.09
P value	0.19		0.58	

3. Results

Among 60 diabetic patients, 25 patients were male. In the patients with positive and negative ETT, 14 and 11 patients were male, respectively. In all patients, mean age was 54.75 \pm 9.37 year, so in the female and male patients were 54.65 \pm 9.07 and 54.88 \pm 9.96 year, respectively ($P = 0.92$). Mean age of female and male patients with positive ETT group were 59.12 \pm 8.26 and 58.28 \pm 10.23 year, respectively ($P = 0.80$) and in the female and male patients with negative ETT were 50.89 \pm 8.12 and 50.54 \pm 8.09 year, respectively ($P = 0.91$). Mean CIMT in all of the patients was 0.82 \pm 0.27 mm; however, in the positive and negative ET groups were 1.04 \pm 0.21 mm and 0.61 \pm 0.11 mm, respectively ($P < 0.001$). There was no significant difference between female and male of positive ETT group based on CIMT, also there was no difference between female and male among the negative ETT group based on CIMT (Table 1).

There was no significant difference between two groups of the patients regarding to FBS, HDL and LDL cholesterol (Table 2). ($P > 0.05$).

4. Discussion

The study showed greater CIMT in diabetic patients with positive ET. CIMT measurement was used for evaluation of micro-vascular and macro-vascular complication of diabetes mellitus. Some studies carried out in this regard with different and controversial result. For example, in the study on 152 type 2 diabetic patients, the association of CIMT with proteinuria was found [27]. In addition, Abdelghaffar and colleagues, in the study on 40 type 1 diabetic patients showed positive association of CIMT with retinopathy and neuropathy [28]. Jung and colleagues in their study on 131 type 2 diabetic patients found no association of CIMT with nephropathy and neuropathy [29]. Discrepancy between the results of mentioned studies may be due to difference in age, duration of diabetes and method of sonography.

About association of CIMT with macrovascular complications of diabetes, there are some other studies. Kota and colleagues in their study showed that CIMT was greater in diabetic patients compare to normal subjects; in addition, CIMT had correlation with LDL cholesterol and history of cerebrovascular accident [30]. Bernard and colleagues in their study on 229 patients with cardiovascular risk, showed that CIMT in the patients with cardiovascular risk was greater than the cases without risk factor [31]. Sensitivity of ETT was estimated about 60% to 70%, and specificity about 60% to 80% in various studies. It has some degree of false positive and false negative results; however, it is an easy, inexpensive, and non-invasive method for evaluation of ischemic heart disease [32,33].

Table 2

Comparison of Mean \pm standard deviation of FBS, HDL and LDL cholesterol in the negative and positive ET patients.

Variable	All patients	Group		P value
		Positive ET	Negative ET	
FBS	145.86 \pm 56.64	136.03 \pm 45.13	155.70 \pm 65.49	0.18
HDL cholesterol	43.85 \pm 9.89	42.54 \pm 11.13	45.16 \pm 8.45	0.30
LDL cholesterol	94.71 \pm 35.94	94.63 \pm 33.48	94.80 \pm 38.82	0.18

Abdushi and colleagues in the study on diabetic patients, found higher CIMT and C-reactive protein (CRP) in patients with acute coronary syndrome and stable angina compared to patients with negative ET [34]. In 87 patients with inconclusive exercise stress test (EST), CIMT and myocardial perfusion imaging study (MPS) were done by C. Y. Karabay and colleagues and they showed higher CIMT in the patients with positive MPS, so they concluded that CIMT may be used as an alternative inexpensive method for evaluation of myocardial ischemia [35]. In addition, Nagai and colleagues in their study on 398 cases with 72 asymptomatic patients with positive ET and 38 known cases of IHD found that CIMT was less in the normal subjects than other groups [36]. The results of above study about association of CIMT and ETT were somehow similar to our results.

In the present study, we did not find the association of CIMT with age and sex of the patients; however, Zhao and colleagues in their study on 355 diabetic patients found the increasing CIMT after 4 years follow-up, as well as higher CIMT in male than female patients [37]. Moreover, in the study of Abdelghaffar and colleagues in type 1 diabetic patients, they found significant correlation of CIMT with age and male sex [28].

In our study, we showed the lack of association of CIMT with FBS, LDL and HDL cholesterol. Similar to our result, Nimkuntod and colleagues in the study on 302 cases found also no association of CIMT with FBS, HDL and LDL cholesterol [38]. In addition, in the study on 62 hemodialysis patients by Abbasi and colleagues, CIMT had not association with fasting blood sugar (EBS) and serum cholesterol [39]. However, Kota reported a significant association of CIMT with FBS and LDL cholesterol [30] Khan and colleagues in the study on 40 familial hyperlipidemic patients showed also an association of CIMT with LDL cholesterol [40]. In Abdelghaffar study, CIMT had also correlation with FBS, and LDL cholesterol [28]. Controversy in the results of mentioned studies may be due to race, age and comorbid diseases of the patients and methodological difference.

The limitations of the study were small sample size and lack of comparison of CIMT with more accurate method such as coronary angiography, so we recommended applying the studies with larger sample size and comparison of results of CIMT with exercise test and coronary artery angiography.

5. Conclusion

The study showed higher CIMT in the diabetic patients with positive ETT, so CIMT may be used as an inexpensive, non-invasive and reliable method for screening and evaluation of IHD in diabetic patients.

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Conflict of interests

The authors had no conflict of interests.

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Research and technology deputy, Shahrekord University of Medical Sciences.

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